CLAIMS

1. An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the predetermined reaction site,

wherein the chip is constructed and arranged to stably connect in a predetermined, aligned relationship to other, similar chips.

2. The apparatus of claim 1, wherein the chip is enclosed.

3. The apparatus of claim 2, wherein the chip has an evaporation rate of less than about 100 microliters per day.

4. The apparatus of claim 3, wherein the chip has an evaporation rate of less than about 50 microliters per day.

5. The apparatus of claim 4, wherein the chip has an evaporation rate of less than about 20 microliters per day.

6. The apparatus of claim 1, wherein the chip has a length of about 128 mm.

7. The apparatus of claim 1, wherein the chip has a width of about 85 mm.

8. The apparatus of claim 1, wherein the chip is able to stably connect to a microplate.

9. An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein the chip is constructed and arranged to be stably connectable to a microplate.

10. The apparatus of claim 9, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

11. The apparatus of claim 9, wherein the chip is enclosed.

12. The apparatus of claim 11, wherein the chip has an evaporation rate of less than about 100 microliters per day.

13. The apparatus of claim 9, wherein the chip has a length of about 128 mm.

14. The apparatus of claim 9, wherein the chip has a width of about 85 mm.

15. The apparatus of claim 9, wherein the microplate comprises at least 6 wells.

16. The apparatus of claim 15, wherein the microplate comprises at least 24 wells.

17. The apparatus of claim 16, wherein the microplate comprises at least 96 wells.

18. The apparatus of claim 17, wherein the microplate comprises at least 384 wells.

19. The apparatus of claim 18, wherein the microplate comprises at least 1,536 wells.

20. The apparatus of claim 9, wherein the microplate substantially conforms with an SBS/ANSI standard.

21. The apparatus of claim 9, wherein the chip is constructed and arranged to address at least one well of the microplate.

22. The apparatus of claim 21, wherein the chip is constructed and arranged to address more than one well of the microplate.

23. An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein the chip is constructed and arranged to be fluid communicable with an apparatus constructed and arranged to address a well of a microplate.

24. The apparatus of claim 23, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

25. The apparatus of claim 23, wherein the chip is enclosed.

26. The apparatus of claim 25, wherein the chip has an evaporation rate of less than about 100 microliters per day.

27. The apparatus of claim 23, wherein the chip is constructed and arranged to address at least one well of the microplate.

28. The apparatus of claim 23, wherein the chip is constructed and arranged to address more than one well of the microplate.

29. An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein each predetermined reaction site overlaps at least one well of a microplate.

30. The apparatus of claim 29, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

31. The apparatus of claim 29, wherein the chip is enclosed.

32. The apparatus of claim 31, wherein the chip has an evaporation rate of less than about 100 microliters per day.

33. The apparatus of claim 29, wherein each predetermined reaction site overlaps exactly one well of a microplate.

34. The apparatus of claim 29, wherein each predetermined reaction site overlaps more than one well of a microplate.

35. An apparatus, comprising:

a substantially liquid-tight chip comprising a predetermined reaction site having a volume of less than about 1 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

36. The apparatus of claim 35, wherein the chip comprises structural components interconnected without auxiliary adhesive at locations defining boundaries of the predetermined reaction site.

37. The apparatus of claim 35, wherein the predetermined reaction site, during use of the chip, is not in fluid communication with an adhesive.

38. An apparatus, comprising:

a chip produced by a process including the step of fastening two components to produce a portion of the chip defining a predetermined reaction site having a volume of less than about 1 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

39. The apparatus of claim 38, wherein the chip is enclosed.

40. The apparatus of claim 38, wherein the two components are fastened without the use of an adhesive material.

41. An apparatus, comprising:

a chip comprising a predetermined reaction site having a volume of less than about 1 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the predetermined reaction site, wherein the predetermined reaction site has a nonzero evaporation rate of less than about 100 microliters/day.

42. The apparatus of claim 41, wherein the chip is enclosed.

43. The apparatus of claim 41, wherein the evaporation rate is less than about 50 microliters per day.

44. The apparatus of claim 43, wherein the evaporation rate is less than about 20 microliters per day.

45. In a method of producing a chip comprising a predetermined reaction site having a volume of less than 1 ml, the improvement comprising:

attaching a first component of the chip to a second component of the chip with or without auxiliary adhesive to produce a portion of the chip that defines the predetermined reaction site.

46. The method of claim 45, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

47. The method of claim 45, wherein the improvement comprises sonic welding the first component to the second component.

48. The method of claim 45, wherein the improvement comprises heat pressing the first component to the second component

49. The method of claim 45, wherein the first component comprises at least one polymer selected from the group consisting of polycarbonate, polysulfone, polyethylene, and blends and copolymers thereof.

50. The method of claim 45, wherein the improvement comprises applying energy to melt at least a portion of the first component.

51. The method of claim 50, wherein the energy comprises ultrasound.

52. The method of claim 50, wherein the energy comprises heat energy.

53. The method of claim 45, wherein the improvement comprises attaching the first component to the second component to produce a liquid-tight junction therebetween.

54. The method of claim 45, wherein the chip is enclosed.

55. An apparatus, comprising:

a predetermined reaction site having a volume of less than about 1 ml; and

a membrane substantially transparent to incident electromagnetic radiation in the infrared to ultraviolet range having a pore size less than 2.0 microns in fluid communication with the predetermined reaction site.

56. The apparatus of claim 55, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

57. An apparatus, comprising:

a predetermined reaction site having a volume of less than about 1 ml, constructed and arranged to carry out a chemical or biological reaction promoted by or monitored by electromagnetic radiation within a predetermined wavelength range; and

a membrane, transparent to electromagnetic radiation within the

predetermined wavelength range to the extent necessary to promote or monitor the reaction, having a pore size of less than 2.0 microns in fluid communication with the predetermined reaction site.

58. The apparatus of claim 57, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

59. The apparatus of claim 57, wherein the membrane is substantially transparent to incident visible electromagnetic radiation.

60. The apparatus of claim 57, wherein the membrane is substantially transparent to incident electromagnetic radiation having a wavelength of between about 400 nm and about 800 nm.

61. The apparatus of claim 57, wherein the membrane has a transparency such that at least 80% of the incident electromagnetic radiation is transmitted across the membrane.

62. The apparatus of claim 61, wherein the membrane has a transparency such that at least 90% of the incident electromagnetic radiation is transmitted across the membrane.

63. The apparatus of claim 62, wherein the membrane has a transparency such that at least 95% of the incident electromagnetic radiation is transmitted across the membrane.

64. The apparatus of claim 57, wherein the membrane has an oxygen permeability of at least about 0.061 mol/day/m^2/atm.

65. The apparatus of claim 57, wherein the membrane has a water permeability of less than about 0.39 mol/day/m^2.

66. An apparatus, comprising:

a chip comprising a first predetermined reaction site having a volume of less than about 1 ml and a second predetermined reaction site, the chip defining a pathway fluidly connecting the first predetermined reaction site and the second predetermined reaction site, wherein the pathway crosses a membrane.

67. The apparatus of claim 66, wherein the first predetermined reaction site is constructed and arranged to maintain at least one living cell at the first predetermined reaction site.

68. The apparatus of claim 66, wherein the chip is enclosed.

69. The apparatus of claim 68, wherein the chip has an evaporation rate of less than about 100 microliters per day.

70. The apparatus of claim 66, wherein the second predetermined reaction site has a volume of less than about 1 ml.

71. The apparatus of claim 66, wherein the membrane is a gas-permeable membrane.

72. The apparatus of claim 71, wherein the gas-permeable membrane is an oxygen-permeable membrane.

73. The apparatus of claim 72, wherein the oxygen-permeable membrane has an oxygen permeability of at least about 0.061 mol/day/m^2/atm

74. The apparatus of claim 71, wherein the gas-permeable membrane is a CO_2-permeable membrane.

75. The apparatus of claim 66, wherein the membrane is porous.

76. The apparatus of claim 75, wherein the membrane has an average pore size of less than about 2 microns.

77. The apparatus of claim 75, wherein the membrane is substantially transparent.

78. The apparatus of claim 66, wherein the membrane is substantially transparent.

79. An apparatus, comprising:

a reaction site having a first portion and a second portion separated by a membrane; and

at least a first and a second channel in fluidic communication with the second portion of the reaction site.

80. The apparatus of claim 79, wherein the reaction site has a volume of less than 2000 microliters.

81. The apparatus of claim 79, wherein the reaction site has a volume of less than 1000 microliters.

82. The apparatus of claim 79, wherein the reaction site has a volume of less than 500 microliters.

83. The apparatus of claim 79, wherein the membrane comprises at least one of polycarbonate, cellulose, nitrocellulose, glass, fiberglass, or polycarbonate, regenerated cellulose, or polyethylene.

84. The apparatus of claim 79, wherein the membrane is permeable to cations and substantially impermeable to anions.

85. The apparatus of claim 79, wherein the membrane is permeable to anions and substantially impermeable to cations.

86. The apparatus of claim 79, wherein the membrane has a pore size less than 10 microns.

87. The apparatus of claim 79, wherein the first channel is fluidly connected to a mixing unit.

88. The apparatus of claim 87, wherein the mixing unit is fluidly connected to at least one inlet.

89. The apparatus of claim 79, wherein the substrate is formed from at least one of a glass, silicon, a metal, and a polymer.

90. The apparatus of claim 79, wherein the second portion of the reaction site is coated with a cytophilic material.

91. The apparatus of claim 79, wherein the first portion of the reaction site comprises a cytophilic material.

92. The apparatus of claim 79, further comprising a temperature sensor in sensing communication with the reaction site.

93. The apparatus of claim 79, further comprising a pH sensor in sensing communication with the reaction site.

94. The apparatus of claim 79, further comprising a pressure sensor in sensing communication with the reaction site.

95. The apparatus of claim 79, further comprising an optical density sensor in sensing communication with the reaction site.

96. The apparatus of claim 79, further comprising a glucose sensor in sensing communication with the reaction site.

97. The apparatus of claim 79, comprising at least 10 reaction sites.

98. The apparatus of claim 97, comprising at least 20 reaction sites.

99. The apparatus of claim 98, comprising at least 50 reaction sites.

100. The apparatus of claim 99, comprising at least 100 reaction sites.

101. The apparatus of claim 79, wherein the first portion is in communication with at least a third channel and a fourth channel.

102. The apparatus of claim 79, wherein the membrane is substantially impermeable to mammalian cells.

103. The apparatus of claim 79, wherein the membrane is substantially permeable to molecules having a molecular weight greater than about 100 kilodaltons.

104. The apparatus of claim 79, wherein the membrane is substantially impermeable to molecules having a molecular weight greater than about 10 kilodaltons.

105. The apparatus of claim 79, wherein the membrane is substantially impermeable to molecules having a molecular weight greater than about 1 kilodalton.

106. A method, comprising:

providing a substrate having a surface into which is fabricated a plurality of reaction sites, at least one reaction site having a volume less than about 2 ml and divided by a substantially cell impermeable membrane into at least a cell culture portion containing cells and a reservoir portion not containing cells, the reservoir portion being fluidly connected to at least a first and a second channel fabricated into the surface of the substrate;

introducing at least one test compound into at least one of the plurality of

reaction sites; and

monitoring the effect of the at least one test compound on cells located within the cell culture portion.

107. The method of claim 106, wherein the membrane allows waste products produced by the cells to enter the reservoir portion.

108. The method of claim 106, wherein the membrane allows a protein produced by the cells to enter the reservoir portion.

109. The method of claim 106, wherein the contents of the reservoir portion is continuously replaced during at least a first period of time.

110. The method of claim 106, wherein the contents of the reservoir portion is periodically replaced during at least a first period of time.

111. The method of claim 106, wherein the cells include prokaryotic cells.

112. The method of claim 106, wherein the cells include eukaryotic cells.

113. The method of claim 106, wherein the membrane is a cation exchange membrane.

114. The method of claim 106, wherein the membrane is an anion exchange membrane.

115. The method of claim 106, wherein the step of monitoring comprises measuring a fluorescent signal influenced by the at least one test compound.

116. The method of claim 106, wherein the cell culture portion comprises a first type of cell and a second type of cell.